

09/806645

JC08 Rec'd PCT/PTO 02 APR 2001

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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PL /US 99/16049

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 A61K31/4468 A61K31/4535 A61K38/33 A61P23/00
 A61L29/00 A61P29/00 //(A61K31/485, 31:138), (A61K31/485,
 31:13), (A61K31/485, 31:445), (A61K31/485, 31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 31358 A (CORNELL RES FOUNDATION INC) 23 July 1998 (1998-07-23) claims 1-5, 11 page 11, line 5-19 page 12, line 16-20 ---	1-3, 5, 7-9, 11, 12, 14-18
X	US 5 635 204 A (GEVIRTZ CLIFFORD ET AL) 3 June 1997 (1997-06-03) claims	9-12, 14, 16
Y	---	1-18
Y	WO 97 10815 A (FROME BRUCE M) 27 March 1997 (1997-03-27) abstract; claims 1, 2 ---	1-18
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 November 1999

Date of mailing of the international search report

24/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KOLESNIKOV Y.A. ET AL: "Peripheral blockade of topical morphine tolerance by ketamine." EUROPEAN JOURNAL OF PHARMACOLOGY, (1999) 374/2 (R1-R2). , XP002121928 abstract	1-3,6, 9-12, 14-18
P,X	KOLESNIKOV Y. ET AL: "Topical opioids in mice: Analgesia and reversal of tolerance by a topical N-methyl-D-aspartate antagonist." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999) 290/1 (247-252). , XP002121929 abstract	1-3,5,6, 9-12, 14-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16049

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
W0 9831358	A	23-07-1998	AU 6244898 A	07-08-1998
US 5635204	A	03-06-1997	NONE	
W0 9710815	A	27-03-1997	NONE	

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

EJ542833587US

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 2955-4006PC

Box No. I TITLE OF INVENTION TOPICAL OPIOID ANALGESIC AND THE REVERSAL OF TOLERANCE BY A TOPICAL NMDA ANTAGONIST

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021
US

☐ This person is also inventor.

Telephone No.
(212) 639-6181

Facsimile No.
(212) 717-3439

Teleprinter No.

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐

all designated States

☒

all designated States except the United States of America

☐

the United States of America only

☐

the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KOLESNIKOV, Yuri
38 Ridge Road
Cresskill, NJ 07626
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

SONNENFELD, Kenneth H. and BROWN, Kathryn M.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
US

Telephone No.

(212) 758-4800

Facsimile No.

(212) 751-6449

Teleprinter No.

421792

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PASTERNAK, Gavril W.
500 E 83rd Street, Apt. 21M
New York, New York 10021
US

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | (continuation-in-part) |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have |
| <input checked="" type="checkbox"/> KZ Kazakhstan | become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LK Sri Lanka | <input type="checkbox"/> |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
 - (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.
3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. V. - Designation of States

US United States of America - continuation-in-part of US
Provisional Patent Application
Serial No. 60/092,982, filed
16 July 1998 (16.07.98)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 16 July 1998 (16.07.98)	60/092,982	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/ EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 5

description (excluding sequence listing part) : 25

claims : 3

abstract : 1

drawings : 6

sequence listing part of description : _____

Total number of sheets : 40

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet (in triplicate)
2. ☒ separate signed power of attorney unsigned
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): Transmittal Letter and Continuation Sheet

Figure of the drawings which should accompany the abstract:

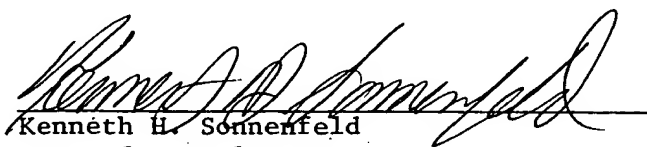
3a

Language of filing of the international application:

English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


Kenneth H. Sonnenfeld
Agent for Applicants

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

Date of receipt of the record copy by the International Bureau:

For International Bureau use only

PCT**FEE CALCULATION SHEET**

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference

2955-4006PC

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER, et al.

CALCULATION OF PRESCRIBED FEES1. TRANSMITTAL FEE \$ 240.00 **T**2. SEARCH FEE \$ 1,002.00 **S**International search to be carried out by EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic FeeThe international application contains 40 sheets.first 30 sheets \$ 455.00 **b1**10 x 10 = \$ 100.00 **b2**

remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B \$ 555.00 **B****Designation Fees**The international application contains 79 designations.10 x 105 = \$ 1,050.00 **D**number of designation fees amount of designation fee
payable (maximum 11)Add amounts entered at B and D and enter total at I \$ 1,605.00 **I**

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) \$ 15.00 **P**

5. TOTAL FEES PAYABLE \$ 2,862.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL☐ The designation fees are not paid at this time.**MODE OF PAYMENT**☐ authorization to charge
deposit account (see below)☐ bank draft☐ coupons☒ cheque☐ cash☐ other (specify):☐ postal money order☐ revenue stamps**DEPOSIT ACCOUNT AUTHORIZATION** (this mode of payment may not be available at all receiving Offices)The RO/ US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.13-450015 July 1999

Deposit Account No.

Date (day/month/year)

Signature

Kenneth H. Sonnenfeld

PATENT COOPERATION TREATY

KMB

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED
PCT
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2000 MAR - 3 P 14:22
**NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY**
(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

To:

SONNENFELD, Kenneth H. et al.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

Date of mailing
(day/month/year)

29.02.00

Applicant's or agent's file reference
2955-4006PC ✓

IMPORTANT NOTIFICATION

International application No.

PCT/US 99/16049 ✓

International filing date (day/month/year)

15/07/1999 ✓

Priority date (day/month/year)

16/07/1998 ✓

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

15/02/2000

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

MORENO R A

Tel. (+49-89) 2399-2658



The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2955-4006PC
International application No. PCT/US99/16049	International filing date (day/month/year) 15 July 1999 (15.07.99)	(Earliest) Priority date (day/month/year) 16 July 1998 (16.07.98)
Title of invention TOPICAL OPIOID ANALGESIC AND THE REVERSAL OF TOLERANCE BY A TOPICAL MNDA ANTAGONIST		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.) Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, New York 10021 US		Telephone No.: (212) 639-6181
		Facsimile No.: (212) 717-3439
		Teleprinter No.:
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.) KOLESKIKOV, Yuri 38 Ridge Road Cresskill, New Jersey 07626 US		
State (that is, country) of nationality: RU		State (that is, country) of residence: US
Name and address: (Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.) PASTERNAK, Gavril W. 500 East 83rd Street, Apt. 21M New York, New York 10021 US		
State (that is, country) of nationality: US		State (that is, country) of residence: US
<input type="checkbox"/> Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)*SONNENFELD, Kenneth H. and BROWN, Kathryn M.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
US

Telephone No.:

(212) 758-4800

Facsimile No.:

(212) 751-6449

Teleprinter No.:

421792

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☐ the international application as originally filed

the description

☐ as originally filed☐ as amended under Article 34

the claims

☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34

the drawings

☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☒ which is the language of a translation furnished for the purposes of international search.☒ which is the language of publication of the international application.☒ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

received not received


<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


Kenneth H. Sonnenfeld
Agent for Applicants

For International Preliminary Examining Authority use only

- Date of actual receipt of DEMAND:
- Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
- ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
 ☐ The applicant has been informed accordingly.
- ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
- ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

<p>International application No. PCT/US99/16049</p> <p>Applicant's or agent's file reference 2955-4006PC</p>	<p>For International Preliminary Examining Authority use only</p> <p>Date stamp of the IPEA</p>								
<p>Applicant</p> <p>Memorial Sloan-Kettering Cancer Center et al.</p>									
<p>Calculation of prescribed fees</p> <p>1. Preliminary examination fee DEM 2998,29 P</p> <p>2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) DEM 287,51 H</p> <p>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</p> <div style="border: 1px solid black; padding: 5px; width: fit-content; margin-left: auto;"> <p>DEM 3285,80</p> <p>TOTAL</p> </div>									
<p>Mode of Payment</p> <table style="width: 100%;"> <tr> <td><input type="checkbox"/> authorization to charge deposit account with the IPEA (see below)</td> <td><input type="checkbox"/> cash</td> </tr> <tr> <td><input checked="" type="checkbox"/> cheque No. 322549218</td> <td><input type="checkbox"/> revenue stamps</td> </tr> <tr> <td><input type="checkbox"/> postal money order</td> <td><input type="checkbox"/> coupons</td> </tr> <tr> <td><input type="checkbox"/> bank draft</td> <td><input type="checkbox"/> other (specify):</td> </tr> </table>		<input type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash	<input checked="" type="checkbox"/> cheque No. 322549218	<input type="checkbox"/> revenue stamps	<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons	<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):
<input type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash								
<input checked="" type="checkbox"/> cheque No. 322549218	<input type="checkbox"/> revenue stamps								
<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons								
<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):								
<p>Deposit Account Authorization (<i>this mode of payment may not be available at all IPEAs</i>)</p> <p>The IPEA/ _____ <input type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account.</p> <p><input type="checkbox"/> (<i>this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.</p>									
<p>Deposit Account Number _____ Date (day/month/year) _____ Signature _____</p>									

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SONNENFELD, Kenneth H. et al.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

WRITTEN OPIN. REPLY DUE
DUE JULY 13, 2000
1 MO CALL-UP JUNE 13, 2000

2955-4006PC KMB

PCT

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference

2955-4006PC✓

Date of mailing
(day/month/year)

13.04.2000

REPLY DUE

within 3 month(s)
from the above date of mailing

International application No.

PCT/US99/16049✓

International filing date (day/month/year)

15/07/1999✓

Priority date (day/month/year)

16/07/1998✓

International Patent Classification (IPC) or both national classification and IPC

A61K31/485

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16/11/2000.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Herrera, S

Formalities officer (incl. extension of time limits)

THORNTON, J

Telephone No. +49 89 2399 8072



WRITTEN OPINION

International application No. PCT/US99/16049

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 9-15, 17-18,

because:

- ☒ the said international application, or the said claims Nos. 9-15, 17-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

WRITTEN OPINION

International application No. PCT/US99/16049

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	9-12,14,16
Inventive step (IS)	Claims	1-18
Industrial applicability (IA)	Claims	1-8,16

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Section III

Claims 9-15 and 17-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

To section V

1. Reference is made to the following documents:
D1: WO-A-9831358
D2: US-A-5635204
D3: WO-A-9710815
D4: European Journal Of Pharmacology, (1999) 374/2 (r1-r2). (0000), , -
D5: Journal Of Pharmacology And Experimental Therapeutics, (1999) 290/1 (247-252).
2. The subject-matter of claims 9-12, 14 and 16 is not considered as novel in that documents D2 discloses the topical use of fentanyl together with ketamine (cf. claim 1). The requirements of Article 33 (2) PCT have therefore not been fulfilled.
3. It is already known to use ketamine topically, both alone (cf. D3) and together with an opiate analgesic (cf. D4). By using this combinations it is inevitable that the tolerance to the opioid does not occur. This means that the skilled man would be able to extend the teachings of D2 and arrive at the subject-matter of the present claims. Therefore the subject-matter of the present claims also lacks the necessary inventive step (Art 33 (3) PCT).
4. For the assessment of the present claims 9-15 and 17-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/US99/16049

and the use of such a compound for the manufacture of a medicament for a new medical treatment.

To section VI

Certain published documents (Rule 70.10)

Depending on the validity on the priority, documents D1, D4 and D5 could become of relevance.



✉ EPA/EPO/OEB
D-80298 München
☎ +49 89 2399-0
TX 523 656 epmu d
FAX +49 89 2399-4465

**Europäisches
Patentamt**

Generaldirektion 2

**Européan
Patent Office**

Directorate General 2

**Office européen
des brevets**

Direction Générale 2

Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

PATENT COOPERATION TREATY

2955-4006 PC
KMBFrom the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYRECEIVED
TICKET DEPT.

2000 NOV

b P 12: 23

PCT

To:

SONNENFELD, Kenneth H. et al.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

MORGAN & FINNEGAN LLP

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)Date of mailing
(day/month/year) 27.10.2000Applicant's or agent's file reference
2955-4006PC ✓

IMPORTANT NOTIFICATION

International application No.
PCT/US99/16049 ✓International filing date (day/month/year)
15/07/1999 ✓Priority date (day/month/year)
16/07/1998 ✓

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Luck, E

Tel. +49 89 2399-8238



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2955-4006PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/16049	International filing date (day/month/year) 15/07/1999	Priority date (day/month/year) 16/07/1998
International Patent Classification (IPC) or national classification and IPC A61K31/485		
Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER et al.		



- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 15/02/2000	Date of completion of this report 27.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrera, S Telephone No. +49 89 2399 8464 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/16049

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 9-15, 17-18.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/16049

- ☒ the said international application, or the said claims Nos. 9-15,17-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 9-12,14,16
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-18
Industrial applicability (IA)	Yes:	Claims 1-8,16
	No:	Claims 9-15,17-18

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/16049

Section III

Claims 9-15 and 17-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:
D1: WO-A-9831358
D2: US-A-5635204
D3: WO-A-9710815
D4: European Journal Of Pharmacology, (1999) 374/2 (r1-r2). (0000), , -
D5: Journal Of Pharmacology And Experimental Therapeutics, (1999) 290/1 (247-252).
2. The subject-matter of claims 9-12, 14 and 16 is not considered novel in that document D2 discloses the topical use of fentanyl together with ketamine (cf. claim 1). The requirements of Article 33 (2) PCT have therefore not been fulfilled.
3. It is already known to use ketamine topically, both alone (cf. D3) and together with an opiate analgesic (cf. D4). By using this combinations it is inevitable that the tolerance to the opioid does not occur. This means that the skilled man would be able to extend the teachings of D2 and arrive at the subject-matter of the present claims. Therefore the subject-matter of the present claims also lacks the necessary inventive step (Art 33 (3) PCT).
4. For the assessment of the present claims 9-15 and 17-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/16049

and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI

Certain published documents (Rule 70.10)

Depending on the validity on the priority, documents D1, D4 and D5 could become of relevance.

PATENT COOPERATION TREATY

PCT

REC'D 31 OCT 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2955-4006PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/16049	International filing date (day/month/year) 15/07/1999	Priority date (day/month/year) 16/07/1998
International Patent Classification (IPC) or national classification and IPC A61K31/485		
Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 15/02/2000	Date of completion of this report 27.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrera, S Telephone No. +49 89 2399 8464



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/16049

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 9-15,17-18.

because:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/16049

- ☒ the said international application, or the said claims Nos. 9-15,17-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	9-12,14,16
Inventive step (IS)	Yes: Claims	
	No: Claims	1-18
Industrial applicability (IA)	Yes: Claims	1-8,16
	No: Claims	9-15,17-18

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/16049

Section III

Claims 9-15 and 17-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V

1. Reference is made to the following documents:
D1: WO-A-9831358
D2: US-A-5635204
D3: WO-A-9710815
D4: European Journal Of Pharmacology, (1999) 374/2 (r1-r2). (0000), , -
D5: Journal Of Pharmacology And Experimental Therapeutics, (1999) 290/1 (247-252).
2. The subject-matter of claims 9-12, 14 and 16 is not considered novel in that document D2 discloses the topical use of fentanyl together with ketamine (cf. claim 1). The requirements of Article 33 (2) PCT have therefore not been fulfilled.
3. It is already known to use ketamine topically, both alone (cf. D3) and together with an opiate analgesic (cf. D4). By using this combinations it is inevitable that the tolerance to the opioid does not occur. This means that the skilled man would be able to extend the teachings of D2 and arrive at the subject-matter of the present claims. Therefore the subject-matter of the present claims also lacks the necessary inventive step (Art 33 (3) PCT).
4. For the assessment of the present claims 9-15 and 17-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/16049

and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI

Certain published documents (Rule 70.10)

Depending on the validity on the priority, documents D1, D4 and D5 could become of relevance.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

Morgan & Finnegan, L.L.P.
Attn. SONNENFELD, K.
345 Park Avenue
New York, New York 10154
UNITED STATES OF AMERICA

Date of mailing
(day/month/year)

24/11/1999

Applicant's or agent's file reference

2955-4006PC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 99/ 16049

International filing date
(day/month/year)

15/07/1999

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Véronique Baillou

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2955-4006PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 16049	International filing date (day/month/year) 15/07/1999	(Earliest) Priority Date (day/month/year) 16/07/1998
Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 99/16049

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 A61K31/4468 A61K31/4535 A61K38/33 A61P23/00
 A61L29/00 A61P29/00 //(A61K31/485, 31:138), (A61K31/485,
 31:13), (A61K31/485, 31:445), (A61K31/485, 31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 31358 A (CORNELL RES FOUNDATION INC) 23 July 1998 (1998-07-23) claims 1-5, 11 page 11, line 5-19 page 12, line 16-20 ---	1-3, 5, 7-9, 11, 12, 14-18
X	US 5 635 204 A (GEVIRTZ CLIFFORD ET AL) 3 June 1997 (1997-06-03) claims	9-12, 14, 16
Y	---	1-18
Y	WO 97 10815 A (FROME BRUCE M) 27 March 1997 (1997-03-27) abstract; claims 1, 2 ---	1-18
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 November 1999

Date of mailing of the international search report

24/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/16049

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KOLESNIKOV Y.A. ET AL: "Peripheral blockade of topical morphine tolerance by ketamine." EUROPEAN JOURNAL OF PHARMACOLOGY, (1999) 374/2 (R1-R2). , XP002121928 abstract ---	1-3,6, 9-12, 14-18
P,X	KOLESNIKOV Y. ET AL: "Topical opioids in mice: Analgesia and reversal of tolerance by a topical N-methyl-D-aspartate antagonist." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999) 290/1 (247-252). , XP002121929 abstract -----	1-3,5,6, 9-12, 14-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16049

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9831358	A	23-07-1998	AU 6244898 A	07-08-1998
US 5635204	A	03-06-1997	NONE	
WO 9710815	A	27-03-1997	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2955-4006PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/16049	International filing date (day/month/year) 15/07/1999	(Earliest) Priority Date (day/month/year) 16/07/1998
Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/16049

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/485 A61K31/4468 A61K31/4535 A61K38/33 A61P23/00
 A61L29/00 A61P29/00 //(A61K31/485,31:138),(A61K31/485,
 31:13),(A61K31/485,31:445),(A61K31/485,31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 31358 A (CORNELL RES FOUNDATION INC) 23 July 1998 (1998-07-23) claims 1-5,11 page 11, line 5-19 page 12, line 16-20 ---	1-3,5, 7-9,11, 12,14-18
X	US 5 635 204 A (GEVIRTZ CLIFFORD ET AL) 3 June 1997 (1997-06-03) claims	9-12,14, 16
Y	---	1-18
Y	WO 97 10815 A (FROME BRUCE M) 27 March 1997 (1997-03-27) abstract; claims 1,2 ---	1-18
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

8 November 1999

Date of mailing of the international search report

24/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/16049

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KOLESNIKOV Y.A. ET AL: "Peripheral blockade of topical morphine tolerance by ketamine." EUROPEAN JOURNAL OF PHARMACOLOGY, (1999) 374/2 (R1-R2). , XP002121928 abstract ---	1-3,6, 9-12, 14-18
P,X	KOLESNIKOV Y. ET AL: "Topical opioids in mice: Analgesia and reversal of tolerance by a topical N-methyl-D-aspartate antagonist." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999) 290/1 (247-252). , XP002121929 abstract -----	1-3,5,6, 9-12, 14-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/16049

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9831358	A	23-07-1998	AU 6244898 A	07-08-1998
US 5635204	A	03-06-1997	NONE	
WO 9710815	A	27-03-1997	NONE	

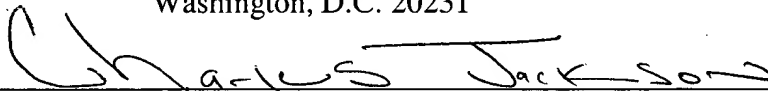
CERTIFICATE OF MAILING - SEPARATE PAPER

"Express Mail" mailing label number: EL 585030083 US

Date of Deposit: March 16, 2001

I hereby certify that this application and the accompanying papers are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to:

Assistant Commissioner for Patents
Box Patent Application (35 USC 111)
Washington, D.C. 20231



(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

FROMMER, LAWRENCE & HAUG LLP
Attn. Lehnhardt, Susan K.
745 Fifth Avenue
NEW YORK, NY 10151
UNITED STATES OF AMERICA

Date of mailing
(day/month/year)

19/06/2002

Applicant's or agent's file reference

830010-2002.

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 01/13546

International filing date
(day/month/year)

27/04/2001

Applicant

MEMORIAL SLOAN-KETTERING CANCER CENTER et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Dominique Hundt

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 830010-2002.	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 01/13546	International filing date (day/month/year) 27/04/2001	(Earliest) Priority Date (day/month/year) 28/04/2000
Applicant MEMORIAL SLOAN-KETTERING CANCER CENTER et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

II INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/13546

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/167 A61K31/485 //(A61K31/485,31:167)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 03716 A (SLOAN KETTERING INST CANCER ;KOLESNIKOV YURI (US); PASTERNAK GAVRI) 27 January 2000 (2000-01-27) page 7, line 7-20; claims 1-14 page 12, line 7-10 page 10, line 33-35	1-35
P,X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 09, 13 October 2000 (2000-10-13) & JP 2000 169378 A (TAISHO PHARMACEUT CO LTD), 20 June 2000 (2000-06-20) abstract -/-	1-3,7,9, 11,12, 21,33

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

6 June 2002

Date of mailing of the international search report

19/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Tardi, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	KOLESNIKOV YURI A ET AL: "Analgesic synergy between topical lidocaine and topical opioids." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 295, no. 2, November 2000 (2000-11), pages 546-551, XP001080389 ISSN: 0022-3565 the whole document ---	1-3,6-9, 11-13, 21,33
A	KHOURY G F ET AL: "INTRAARTICULAR MORPHINE, BUPIVACAINE, AND MORPHINE/BUPIVACAINE FOR PAIN CONTROL AFTER KNEE VIDEOARTHROSCOPY" ANESTHESIOLOGY, AMERICAN SOCIETY OF ANESTHIOLOGISTS, PHILADELPHIA, PA.,, US, vol. 77, no. 263, 1992, pages 263-266, XP000910063 ISSN: 0003-3022 the whole document ---	
A	KANEKO MEGUMI ET AL: "Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats." ANESTHESIOLOGY, vol. 80, no. 1, 1994, pages 137-150, XP001080405 ISSN: 0003-3022 the whole document ---	
A	SAITO YOJI ET AL: "Interaction of intrathecally infused morphine and lidocaine in rats (Part I)." ANESTHESIOLOGY (HAGERSTOWN), vol. 89, no. 6, December 1998 (1998-12), pages 1455-1463, XP001080402 ISSN: 0003-3022 the whole document ---	
A	ATANASSOFF PETER G ET AL: "The effect of intradermal administration of lidocaine and morphine on the response to thermal stimulation." ANESTHESIA & ANALGESIA, vol. 84, no. 6, 1997, pages 1340-1343, XP001079098 ISSN: 0003-2999 the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/13546

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/13546

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0003716	A	27-01-2000	AU 4998799 A BR 9912827 A CN 1309562 T EP 1102589 A1 WO 0003716 A1	07-02-2000 02-05-2001 22-08-2001 30-05-2001 27-01-2000
JP 2000169378	A	20-06-2000	NONE	